# Vaccine-induced immune thrombotic thrombocytopenia following AstraZeneca (ChAdOx1 nCoV-19) vaccine: report of two cases

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**ABSTRACT**

Vaccination with ChAdOx1 nCoV-19 can result in vaccine-induced immune thrombotic thrombocytopenia (VITT). This phenomenon mimics heparin-induced thrombocytopenia, yet it does not require heparin as a trigger. This case report highlights the potentially life-threatening complication associated with ChAdOx1 nCov-19 vaccine, clinical presentation, diagnostic approach, and treatment. We report two cases of vaccine-induced immune thrombotic thrombocytopenia after receiving the first dose of the ChAdOx1 nCoV-19 vaccine. We attribute these thrombotic conditions to the vaccine due to the remarkable temporal relationship. The proposed mechanism of VITT is a production of antibodies against platelet factor-4 resulting in massive platelet activation. Healthcare providers should be aware of the possibility of such a fatal complication, and the vaccine recipients should be warned about the symptoms of VITT.

## INTRODUCTION

The Coronavirus Disease 2019 (COVID-19) pandemic has affected health and economic systems globally. Shortly after the first case series was reported in China,[1] the number of new cases increased exponentially. COVID-19 is a serious infectious disease with a high mortality rate of up to 3.4% among infected patients.[2] Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS_CoV-2) are the most important countermeasure to fight the COVID-19 pandemic. From December 2020 through March 2021, the European Medicines Agency approved four vaccines on the basis of randomized, blinded, controlled trials:[3] two messenger RNA-based vaccines (Pfizer-BioNTech and Moderna) that encode the spike protein antigen of Sars-CoV-2, encapsulated in lipid nanoparticles; and two adenoviral-vector based vaccines, encoding the SARS-CoV-2 spike glycoprotein, ChAdOx1 nCoV-19 (Vaxzervria, AstraZeneca), with a recombinant chimpanzee adenoviral vector and Ad26.COV2.S (Johnson & Johnson/Jassen), with a recombinant adenovirus type 26 vector. In Italy, vaccination was started in January 2021, with most adverse event reports indicating minor side effects. However, some individuals receiving the ChAdOx1 nCoV-19 vaccine, developed a vaccine type-specific complication named vaccine-induced immune thrombotic thrombocytopenia (VITT) within 4-28 days after the first dose of vaccine.[4-6] The mortality rate of VITT was high and reached 18% (71 of 390) in the United Kingdom.[7] It has been assumed that the mechanisms of VITT and autoimmune/spontaneous heparin-induced thrombocytopenia/thrombosis (HIT/T) are similar.[6] We present here two cases of VITT which have come to our observation. Both cases did not present with the more common cerebral venous thrombosis.

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## CASE REPORT #1

We report a case of a 45-year-old male patient who, 8 days after the ChAdOx1 nCoV-19 vaccine, presented to the emergency room (ER) for precordial pain. A non-

ST elevation myocardial infarction (non-STEMI) heart attack was diagnosed. Coronary angiography diagnosed coronary thrombosis on uninjured coronaries. A drug-eluting stent was placed, but 6 hours after the procedure the patient experienced acute closure, treated with plain old balloon angioplasty (POBA). Later, extensive intraventricular thrombosis was diagnosed. The patient was treated with double antiplatelet therapy and enoxaparin was started. After a further 4 days, due to pain in the lower limbs appeared two days after POBA, computed tomography (CT) with angiography was performed which highlighted: thrombotic occlusion of the common right femoral artery and popliteal left, critical thrombotic stenosis of the external iliac arteries bilaterally, the hypogastric artery and the anterior tibial right, and occlusion of a branch of the right hepatic vein at the hepatic segment. There were also multiple splenic and bilateral renal infarcts. A Fogarty catheter embolectomy at the level of the common femoral artery right was then performed.

Three days prior to vaccine administration the platelet count was $280\times10^3$/μL. On admission in ER the platelets count was halved ($163\times10^3$/μL). Five days after drug-eluting stent placement and one day after embolectomy, the platelet count was $55\times10^3$ Ul. Finally, tests HIT (Werfen, Barcelona, Spain) were carried out at our center that excluded the presence of heparin PF4 antibodies (0.01 U/ml; normal value 0-1 U/ml), but at the time of the examination the platelets were already increasing. However, it should be noted that these tests are often false negative. It was not possible to perform functional platelet activation assay, heparin-induced platelet aggregation (HIPA). Except for the DDimer, all other tests, including investigations for thrombophilia, were normal.

The patient switched to fondaparinux therapy and started dexamethasone 40 mg/kg body weight for 4 days. Three months after the onset of symptoms, the platelet count is normal, $335\times10^3$/μL; the patient has fully recovered, and he is fine.

## CASE REPORT #2

We describe a case of concomitant thrombosis of portal, superior mesenteric and splenic veins in a 49-year-old female patient, with no known risk factors, who had received ChAdOx1 nCoV-19 vaccine, 7 days before.

The patient went to the ER for abdominal pain and melaena. At the time of admission, laboratory data showed prolonged prothrombin time (PT) and activated partial thromboplastin time (aPTT), significant reduction of plasma fibrinogen (30 mg/dl) and platelet count ($30\times10^3$ Ul) (Table 1).

CT revealed filling defects in the entire spleno-portal axis with extension also to the intrahepatic portal branches, to the splenic vein and to the superior mesenteric vein; and the presence of flap of peritoneal effusion. The patient presented with an episode of extreme bradycardia which required resuscitation. The next day the laboratory data from blood sampling sent to our center showed positivity for heparin-PF4 antibodies (1,55 U/ml), low platelet count ($32\times10^3$/μL), confirming abnormalities of PT (PT 41%; INR 1.93), aPTT (aPTT 42.2 sec; ratio 1.33) , and fibrinogen levels (116 mg/dl), together with significantly elevated DDimer (61697 ng/ml), reduced levels of protein C and protein S, lupus anticoagulant slightly positive, but not univocal interpretation, anticardiolipin antibodies and Beta-2 glycoprotein 1 (B2GP1) antibodies negative, absence of Factor V Leiden and Factor II G20210A mutation.

Treatment with fondaparinux, intravenous high dose immunoglobulins, methylprednisolone and replacement therapy with antithrombin, fibrinogen concentrate, and prothrombin complex concentrate were initiated.

Ten days after the event, the patient was in intensive

**Table 1.** Temporal correlation between platelet count and thrombosis.

| | Basal platelet count, U/ml | Vaccine | Hospitalization, U/ml | 1 dpost-H, U/ml | 3 dpost-H, U/ml | 5 dpost-H, U/ml | 8 dpost-H, U/ml | 11 dpost-H, U/ml | 13 dpost-H, U/ml | 17 dpost-H, U/ml |
|---|---|---|---|---|---|---|---|---|---|---|
| Pz 1 | $280\times10^3$ | - | $163\times10^3$ | $152\times10^3$ | $118\times10^3$ | $55\times10^3$ | $76\times10^3$ | $85\times10^3$ | $142\times10^3$ | $164\times10^3$ |
| Pz 1 thrombosis | - | - | 8 days after the vaccine N-STEMI | Acute-stent closure | - | All other thrombosis | - | - | - | - |
| Pz 2 | - | - | $30\times10^3$ | $32\times10^3$ | - | - | - | - | - | $152\times10^3$ |
| Pz 2 thrombosis | - | - | 7 days after the vaccine SVT | - | - | - | - | - | - | Death |

*H, hospitalization; N-STEMI, non-ST elevation myocardial infarction; SVT, splanchnic vein thrombosis.*

care unit, sedated and intubated, she had renal insufficiency, heparin-PF4 antibodies negative, platelet count and blood clotting parameters normalized. However, the patient died 18 days after the onset of symptoms.

## DISCUSSION

Since the first reports of case series were published in April 2021, the number of patients diagnosed with VITT associated with the ChAdOx1 nCoV-19 vaccine developed by AstraZeneca has grown and continues to grow.[4-6] The Ad26.COV2.S vaccine (Johnson & Johnson) with similar adenovirus viral vector technology, was also reported to induce thrombocytopenia and thrombosis in the United States.[7]

Most patients with VITT present with thrombosis at unusual sites, such as the cerebral venous sinus or the splanchnic vein, with concomitant severe thrombocytopenia.[4-7] Thrombosis reported are predominantly venous thrombosis, but sporadic cases of arterial thrombosis are also reported.[8-12] The onset of VITT is usually 4–28 days after vaccination.[4-7] Although the exact pathogenesis and risk factors of VITT are still unknown, many laboratory findings support the hypothesis that the mechanism of thrombocytopenia and thrombosis is similar to that of autoimmune HIT/T in that the anti-PF4 antibody may be induced by polyanions, including lipid A, in bacterial surface nucleic acids instead of heparin.[6] For VITT, some components of the vaccine, for example, the adenovirus DNA, spike protein, and/or neoantigen induced by the vaccine, have been proposed to be key components that could induce PF4 release and anti-PF4 antibody production.[13]

In our first case we cannot entirely exclude that we are faced with a HIT, but there are some considerations to be made. At the time of admission in ER, even before any therapy, the patient had platelet values almost halved, compared to the platelet count taken immediately before the vaccine ($280\times10^3$/mmc → $163\times10^3$/mmc. Furthermore, the patient had no risk factors for heart attack and on coronary angiography there was a coronary artery thrombosis on uninjured coronaries. He immediately underwent PTCA with drug eluting stent placement, with fondaparinux, lysine acetylsalicylate and then concomitant administration of cangrelor and ticagrelor. After only 6 hours from stent placement, pain in the shoulder and left arm with evidence of ST displacement and acute stent closure. POBA was performed and only after this second maneuver therapy with enoxaparin was started. Immediately after there was echocardiographic evidence of multiple extensive apical thrombotic manifestations.

Two days after POBA (30 hours after the admission to ER), pain in the lower limbs and abdomen appeared, which worsened the next day, becoming more and more intense, but unfortunately the angio-CT which showed all other thromboses was only performed after a further two days. Therefore, although it is not possible to exclude heparin-induced thrombocytopenia, it should be emphasized that the temporal criterion would not be respected (the patient would have presented arterial thrombotic manifestations and splenic infarcts after only 2 days from the start of enoxaparin, while the heart attack, stent closure and intraventricular thrombosis would have occurred prior to the administration of enoxaparin). The patient had never previously been treated with heparin; therefore, rapid onset is not justified. These are the reasons why we believe that the diagnosis of VITT is more likely than that of HIT.

VITT is a rapidly fatal disorder if not recognized and treated early. A recent post-mortem report showed extensive involvement of large venous vessels with thrombotic occlusions in the microcirculation of multiple organs. These findings indicated the progression of an inflammatory process that culminates in microvascular injury of multiple organs by iatrogenic activation of the innate immune system along with the complement pathway.[14]

The Italian Society for the Study of Hemostasis and Thrombosis – SISET, as well as other scientific societies, have provided some recommendations based on the consensus of experts for the management of cerebral and splanchnic venous thrombotic events associated with thrombocytopenia occurred in subjects vaccinated within 30 days with the Vaxzervria vaccine.[15] In accordance with these recommendations, we have diagnosed and managed two cases of VITT. Both the patients presented to hospital 1-2 weeks after their first dose of the AstraZeneca vaccine, although the second patient was hospitalized three days after the onset of symptoms. Positive anti-PF4 antibodies were detected only in one of two cases, probably due to the delay in sending the sample for determination of anti-PF4 antibodies. In neither case was it possible to carry out the HIPA confirmation test. Both patients were treated with a non-heparin anticoagulant and dexamethasone.

## CONCLUSIONS

Clinicians must be alerted to the possibility of such a precipitously fatal complication while vaccine recipients should be warned about the symptoms of VITT. The rapid recognition of the pathology is fundamental, in fact prompt treatment can improve the patient's outcome. More research data, data collections, reports, registries, especially about the risk factors and pathogenesis of the syndrome, are needed to encourage patients to be vaccinated confidently.

In Italy, the SISET VAX COVID 19 study promoted by SISET aims to consecutively record all thrombosis events associated or not associated with thrombocytopenia arising after vaccines against SARS-CoV-2, to collect as much information as possible on the events, to ade-

quately characterize them, provide useful data for the formulation of pathogenetic hypotheses and for the design of any intervention studies.[16]

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